(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2003 (19.06.2003)

PCT

(10) International Publication Number
WO 03/050124 A1

(51) International Patent Classification[7]: C07D 501/22, A61K 31/546

(21) International Application Number: PCT/IB02/05315

(22) International Filing Date:
12 December 2002 (12.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1242/DEL/2001 13 December 2001 (13.12.2001) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi 110 019 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUMAR, Yatendra** [IN/IN]; U-26/5, Phase - III, DLF Qutab Enclave, Gurgaon 122 001, Haryana (IN). **PRASAD, Mohan** [IN/IN]; P-3/3, Phase - II, DLF Qutab Enclave, Gurgaon 122 001, Haryana (IN). **PRASAD, Ashok** [IN/IN]; 147/9, Dr. Gupta's Flat, Kishangarh, Vasant Kunj, New Delhi 110 070 (IN). **SINGH, Shailendra, Kumar** [IN/IN]; A-35/30, Phase-I, DLF Qutab Enclave, Gurgaon 122 001, Haryana (IN). **KUMAR, Neela, Praveen** [IN/IN]; House No. 16-2-705/9/A/8, Professors Colony, Malakpet, Hyderabad 500 036, Andhra Pradesh (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; DESHMUKH, Jayadeep, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CRYSTALLINE CEFDINIR POTASSIUM DIHYDRATE

(57) Abstract: The present invention relates to a novel crystalline cefdinir potassium dihydrate, to a process for its preparation and to a method of preparing pure cefdinir via the crystalline salt.

WO 03/050124 A1

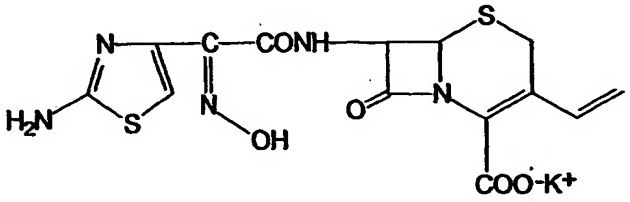
CRYSTALLINE CEFDINIR POTASSIUM DIHYDRATE

Field of the Invention

The present invention relates to a novel crystalline cefdinir potassium dihydrate, to a process for its preparation and to a method of preparing pure cefdinir via the crystalline salt.

Background of the Invention

Cefdinir potassium is chemically known as potassium 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) of formula I,



FORMULA I

and was described for the first time in U.S. Patent No. 4,559,334. Cefdinir is a third generation cephalosporin antibiotic for oral administration and has a broader antibacterial spectrum than other orally administrable antibiotics. Cefdinir is particularly effective against staphylococci and streptococci.

U.S. Patent No. 4,559,334 describes the preparation of cefdinir sodium and its isolation via chromatography followed by lyophilization. The salt obtained according to the procedure in said U.S. Patent is amorphous and hygroscopic, and therefore it is not suitable for a pharmaceutical product or is not easy to handle in the pharmaceutical preparations, in producing it on a commercial scale or in storage.

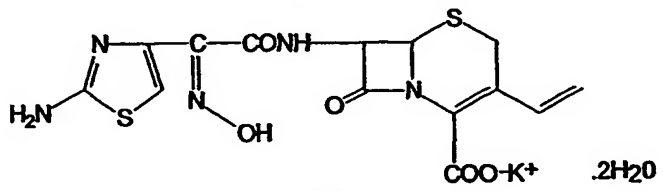
Therefore, there is a need for pure and stable crystalline salts of cefdinir, which are suitable for pharmaceutical preparations.

Summary of the Invention

We have now found that potassium salt of cefdinir can be obtained as a pure crystalline dihydrate, which can be prepared by a simple and efficient process. This crystalline salt may be conveniently formulated into tablets, suspensions, injectables and other pharmaceutical forms. Furthermore, it has been found that an efficient purification of cefdinir may be achieved by crystallizing it as cefdinir potassium dihydrate and then converting it to pure cefdinir.

Detailed Description of the Invention

The present invention provides a novel crystalline cefdinir potassium dihydrate of structural formula II. The characteristic IR and XRD spectra of cefdinir potassium dihydrate are given in Figure I and II, respectively.



FORMULA II

The present invention also provides a process for preparing cefdinir potassium dihydrate which comprises obtaining a solution of cefdinir potassium in a suitable solvent and crystallizing cefdinir potassium dihydrate from a solution thereof. The solution of cefdinir potassium can be obtained by adding a potassium salt of a weak acid to a suspension or solution of cefdinir in a suitable solvent. The solution of cefdinir may be obtained either by dissolving cefdinir in a suitable solvent or directly from a reaction in which cefdinir is formed.

Often, when the potassium salt of a weak acid is added to a suspension of cefdinir in a suitable solvent the cefdinir potassium dihydrate starts crystallizing out even before cefdinir has gone into solution completely. Such a process is within the meaning of the process of the present invention.

Cefdinir used as the starting material may be obtained by any of the methods known in the prior art, for example, as described in U.S. Patent Nos. 4,559,334; 4,870,168; 6,093,814; or as described in WO 92/7840, Japanese Patent applications 4/173781; 1/238587, and 2/000790 and are incorporated herein by reference.

The weak acid whose potassium salt may be used for forming potassium salt of cefdinir may be either an organic acid or an inorganic acid. Examples of suitable potassium salts include potassium acetate, potassium carbonate, potassium bicarbonate, and the like.

As per the present invention, the term "suitable solvent" may be any water miscible organic solvent in admixture with water. Suitable water miscible organic solvents include ketones such as acetone, ethylmethyl ketone; lower alcohols such as methanol, ethanol, propanol, isopropanol; nitriles such as acetonitrile; cyclic ethers such as tetrahydrofuran, dioxane, and mixture(s) thereof.

The crystallization may be performed at any suitable temperature depending on the solvent used. However, crystallization is preferably performed at about 0°C to about 30°C, or preferably at about 5°C to about 10°C.

In another aspect, the invention provides a process for the preparation of pure cefdinir which comprises preparing crystalline cefdinir potassium dihydrate of crude cefdinir, optionally recrystallized one or more times, and converting it to a free acid i.e. cefdinir. The product may be obtained as crystal A as described in U.S. Patent No. 4,935,507, which is incorporated herein by reference. Alternatively, amorphous form of cefdinir similar to that produced by the method described in U.S. Patent No. 4,559,334 may also be obtained via the purification process of the present invention.

The conversion of cefdinir potassium dihydrate to cefdinir can be accomplished by dissolving cefdinir potassium dihydrate in water and acidifying it to obtain the free acid, cefdinir.

"Crude cefdinir" is cefdinir prepared by any of the methods known in the prior art, which may contain anti-isomer, polymeric impurities or any other impurity which may

arise during production or storage, such as degradation products. Crude cefdinir may be a solid or it may exist in a solvent e.g. in a mixture resulting directly from a reaction for the synthesis of cefdinir.

Cefdinir obtained by the process of the present invention has a purity greater than 99%.

In yet another aspect, the present invention also provides pharmaceutical compositions comprising cefdinir potassium dihydrate or cefdinir in combination with a pharmaceutical acceptable carrier and optionally included excipients, or diluents.

In the following section preferred embodiments are described by way of examples to illustrate the process of the invention. However, these are not intended in any way to limit the scope of the present invention.

Process for Preparing Cefdinir Potassium Dihydrate

EXAMPLE 1

Potassium 7-(Z)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate, dihydrate.

To a suspension of cefdinir (5g) in a mixture of water (25ml) and acetone (25ml) was added potassium acetate (1.75g) at 25-30°C. The reaction mixture was stirred at this temperature for 2-3 hours for complete salt formation. The product started crystallizing out within about half an hour of potassium acetate addition. The reaction mixture was then cooled to 5-10°C and stirred for 1.5 hours. The crystals were filtered, washed with acetone and dried to obtain 5.4g of the title compound.
Yield 91%, HPLC purity: 99.85%, Water (w/w): 8.1%, K-content (w/w): 8.3%

^{1}H- HMR (DMSO-d_6, 300MHz): 11.4 (H, s), 9.42 (1H, d, j=8.1Hz), 7.16 (2H, s), 6.99 (1H, dd, j=11.1Hz, 17.7Hz), 6.64 (1H, s), 5.6(1H, dd, j=4.8Hz, 8.1Hz), 5.14 (1H, d, j=17.7Hz) 5.03(1H, d, j=4.8Hz), 4.93 (1H, d, j=11.4Hz), 3.4-3.8 (4H, m,).
IR (KBr, cm^{-1}): 3261, 1757, 1669, 1617, 1586.

EXAMPLE 2

Potassium 7-(Z)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate, dihydrate

Cefdinir (5g) was suspended in a mixture of water (25ml) and isopropanol (25ml) at 25-30°C. Potassium acetate (1.75g) was added to this suspension and stirred for 2-3 hours for complete salt formation. The crystals were filtered, washed with acetone and dried to obtain 5.1g of the title compound (Yield 86%, HPLC Purity: 99.5%).

Process for Preparing Pure Cefdinir

EXAMPLE 3

Potassium 7-(Z)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate, dihydrate

Crude cefdinir (25g, purity 94.5%) was suspended in a mixture of water (125ml) and acetone (125ml) at 25-30°C. Potassium acetate (8.75g) was added to this suspension and stirred for 2-3 hours for complete salt formation. The crystals were filtered, washed with acetone and dried to obtain 22.5g of the title compound (Yield 76%, HPLC Purity: 99.5%).

EXAMPLE 4

7-(Z)-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]—3-vinyl-3-cephem-4-carboxylic acid (cefdinir)

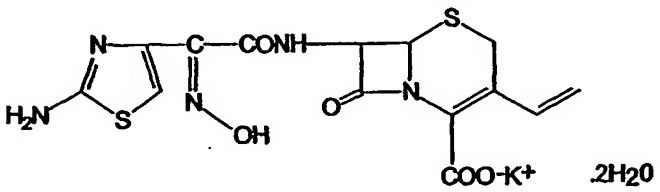
Cefdinir potassium dihydrate (10g) obtained from example 3 was dissolved in water (250ml) at 30-35°C. Active carbon (1g) and sodium metabisulfite (0.5g) were added to the resulting solution and the mixture was stirred for 25-30 minutes at 30-35°C. It was filtered through celite and pH of the solution was adjusted to 2.4 – 2.6 at 30°C and stirred at this temperature to obtain crystalline cefdinir (Yield 7.6g, HPLC purity: 99.5%).

IR (KBr, cm^{-1}): 3295, 1767, 1683, 1622, 1519.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

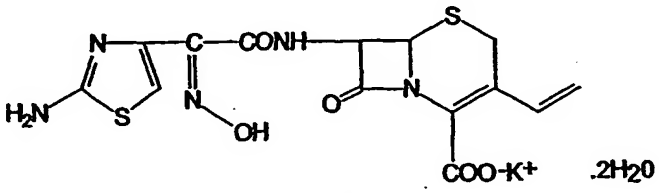
CLAIMS:

1. Crystalline cefdinir potassium dihydrate of structural formula II.



FORMULA II

2. A process for the preparation of cefdinir potassium dihydrate of formula II



FORMULA II

which comprises obtaining a solution of cefdinir potassium in a suitable solvent and crystallizing cefdinir potassium dihydrate from a solution thereof.

3. The process of claim 2 wherein the solution of cefdinir potassium is obtained by adding a potassium salt of a weak acid to a suspension or solution of cefdinir in said suitable solvent.

4. The process of claim 3 wherein the solution of cefdinir is obtained directly from a reaction in which cefdinir is formed.

5. The process of claim 2 wherein the potassium salt of a weak acid is selected from the group consisting of potassium acetate, potassium carbonate, and potassium bicarbonate.

6. The process of claim 2 wherein the suitable solvent is a water miscible organic solvent in admixture with water.

7. The process of claim 6 wherein the water miscible organic solvent comprises a ketone, lower alcohol, nitrile, cyclic ether and mixture(s) thereof.

8. The process of claim 7 wherein the ketone is acetone, ethyl methyl ketone and a mixture thereof.

9. The process of claim 7 wherein the lower alcohol is methanol, ethanol, propanol, isopropanol, and a mixture thereof.

10. The process of claim 7 wherein the nitrile is acetonitrile.

11. The process of claim 7 wherein the cyclic ether is tetrahydrofuran, dioxane and a mixture thereof.

12. The process of claim 2 further comprises converting crystalline cefdinir potassium dihydrate to cefdinir by treatment with an acid.

13. The process of claim 12 wherein the crystalline cefdinir potassium dihydrate is dissolved in water before treatment with an acid.

14. A process for the preparation of pure cefdinir which comprises preparing crystalline cefdinir potassium dihydrate of crude cefdinir, and converting it to cefdinir.

15. The process of claim 14, wherein the crude cefdinir is in solution which is obtained directly from a reaction for the synthesis of cefdinir.

16. Pure cefdinir prepared by the process of claim 14.

17. Cefdinir of claim 16 having a purity of more than 99%.

18. A pharmaceutical composition comprising cefdinir of claim 16 together with pharmaceutically acceptable carriers, excipients or diluents.

19. A pharmaceutical composition comprising cefdinir potassium dihydrate together with pharmaceutically acceptable carriers, excipients or diluents.

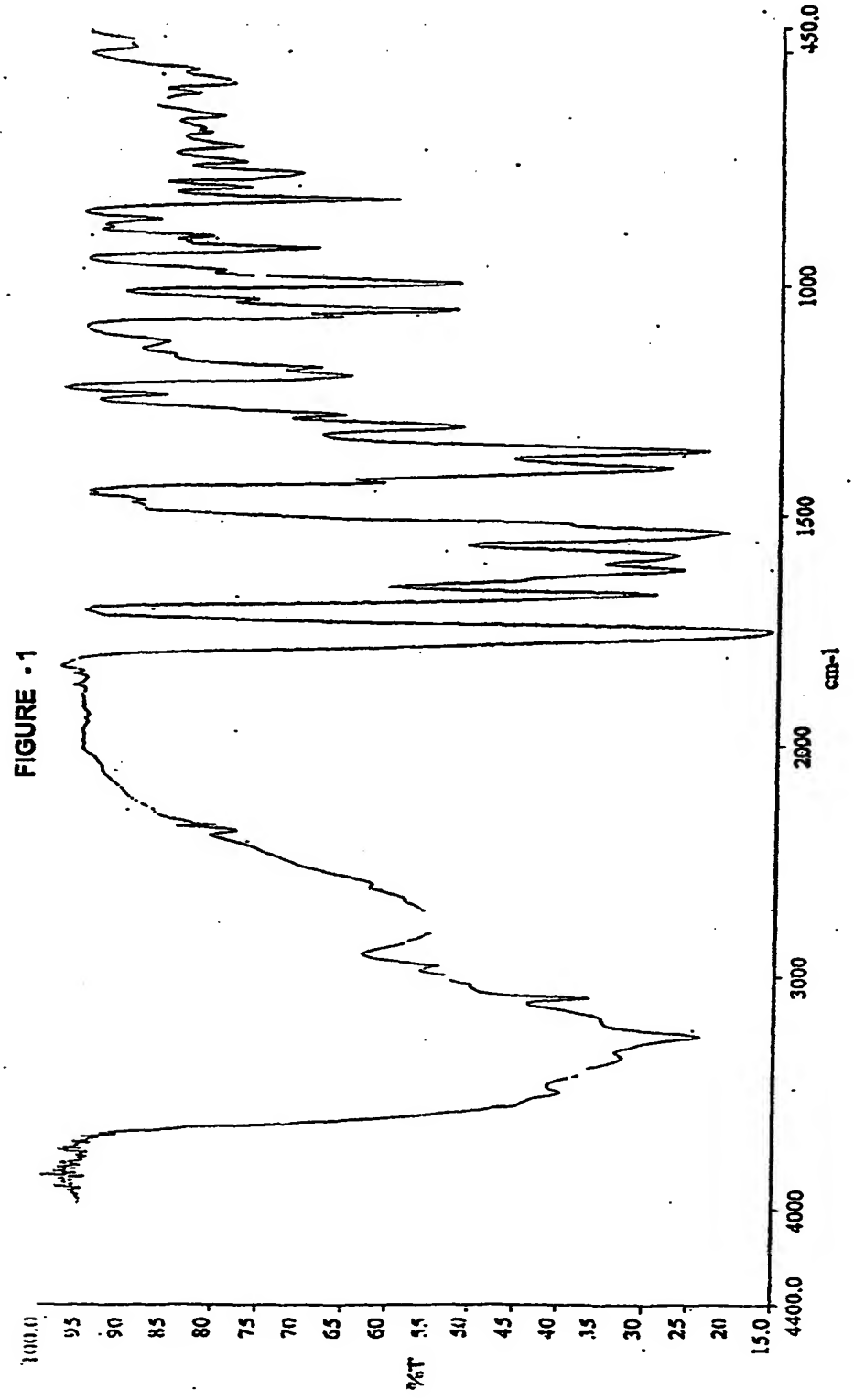
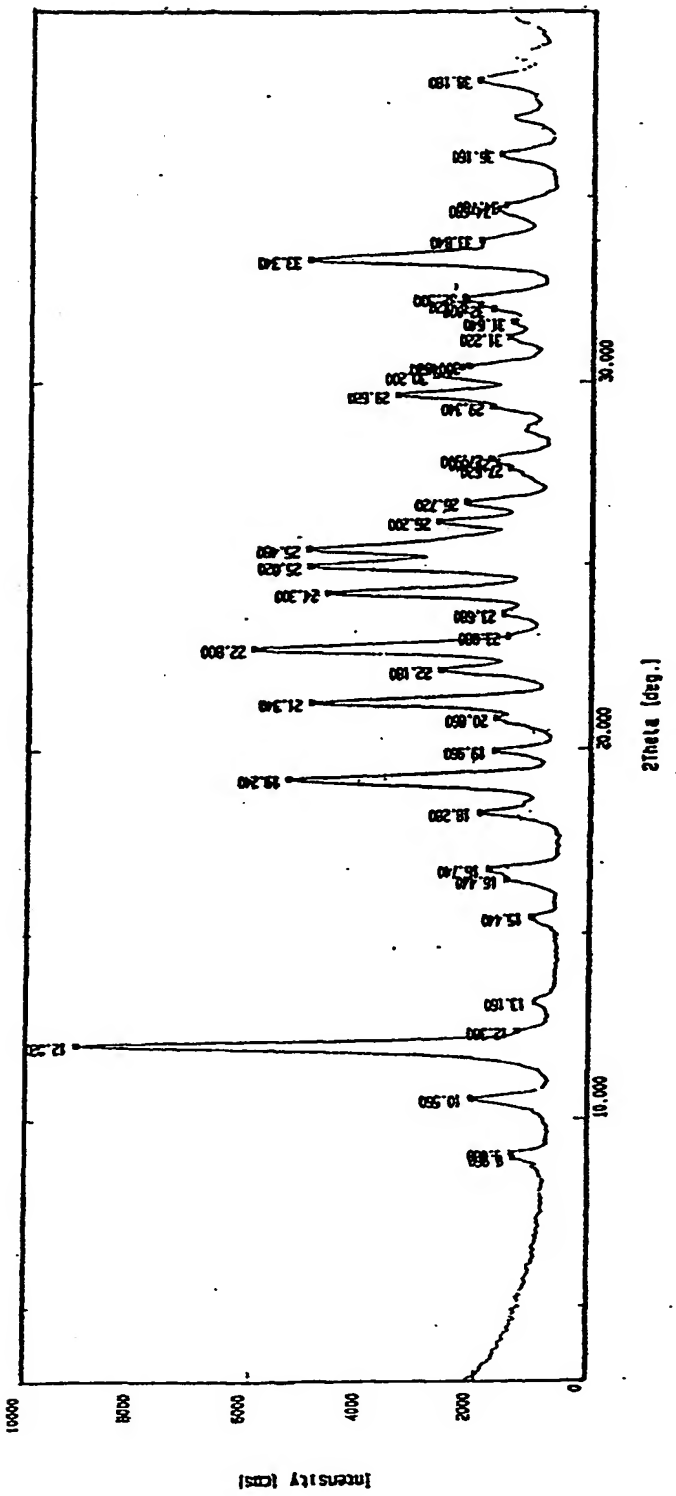

%T
100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15.0
4400.0
4000
3000
2000
1500
1000
450.0
cm-1

FIGURE - 1

FIGURE - 2


Intensity [cps]
10000
8000
6000
4000
2000
0
2Theta [deg.]
10.000
20.000
30.000
12.220
10.550
9.880
13.160
15.440
16.740
18.260
19.960
21.340
22.180
22.800
23.880
24.300
25.820
25.460
26.200
26.720
29.340
31.220
31.640
33.340
35.160
36.180

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/IB 02/05315

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/22 A61K31/546

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 304 019 A (FUJISAWA PHARMACEUTICAL CO) 22 February 1989 (1989-02-22) page 7, line 41-43; claims 1,3,7,10; examples 1,3,4	1-3,14, 18
Y	WO 00 05233 A (SANOFI SYNTHELABO ;RADISSON JOEL (FR)) 3 February 2000 (2000-02-03) claims; examples 1-3,5-7	1-3,14, 18
A	WO 97 24358 A (HANMI PHARMACEUTICAL CO LTD ;LEE GWAN SUN (KR); CHANG YOUNG KIL (K) 10 July 1997 (1997-07-10) claims	1
A	US 4 559 334 A (KAWABATA KOHJI ET AL) 17 December 1985 (1985-12-17) cited in the application the whole document	1-19

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2003	27/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/IB 02/05315

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 098884 A (CHANG YOUNG KIL ;KIM CHEOL KYUNG (KR); KIM HONG SUN (KR); LEE GWAN) 12 December 2002 (2002-12-12) claims 8-11; example 3	1-4,14, 18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/IB 02/05315

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0304019 A	22-02-1989	AT 123221 T	15-06-1995
		AU 617347 B2	28-11-1991
		CA 1297096 A1	10-03-1992
		DE 3853901 D1	06-07-1995
		DE 3853901 T2	12-10-1995
		EP 0304019 A2	22-02-1989
		ES 2072856 T3	01-08-1995
		HK 18496 A	09-02-1996
		IE 67348 B1	20-03-1996
		JP 1250384 A	05-10-1989
		JP 1943842 C	23-06-1995
		JP 6074276 B	21-09-1994
		KR 9708126 B1	21-05-1997
		MX 9203468 A1	01-09-1992
		US 4935507 A	19-06-1990
		ZA 8805709 A	26-04-1989
WO 0005233 A	03-02-2000	FR 2781227 A1	21-01-2000
		AT 218565 T	15-06-2002
		AU 4628799 A	14-02-2000
		CA 2338013 A1	03-02-2000
		DE 69901710 D1	11-07-2002
		EP 1098895 A1	16-05-2001
		WO 0005233 A1	03-02-2000
		JP 2002521383 T	16-07-2002
		US 6365748 B1	02-04-2002
WO 9724358 A	10-07-1997	KR 174432 B1	18-02-1999
		KR 174431 B1	18-02-1999
		AT 218572 T	15-06-2002
		DE 69621649 D1	11-07-2002
		DE 69621649 T2	19-09-2002
		DK 874853 T3	23-09-2002
		EP 0874853 A1	04-11-1998
		ES 2175167 T3	16-11-2002
		JP 2000502700 T	07-03-2000
		WO 9724358 A1	10-07-1997
		PT 874853 T	30-09-2002
		US 6093814 A	25-07-2000
US 4559334 A	17-12-1985	AT 381497 B	27-10-1986
		AT 342783 A	15-03-1986
		AT 385994 B	10-06-1988
		AU 576735 B2	08-09-1988
		AU 1927783 A	05-04-1984
		CA 1206956 A1	01-07-1986
		CH 657857 A5	30-09-1986
		DE 3379463 D1	27-04-1989
		DK 427083 A ,B,	31-03-1984
		EP 0105459 A2	18-04-1984
		ES 8600309 A1	01-01-1986
		ES 8800235 A1	01-01-1988
		FI 833370 A ,B,	31-03-1984
		FR 2533926 A1	06-04-1984
		GB 2127812 A ,B	18-04-1984
		GR 79674 A1	31-10-1984
		HU 190166 B	28-08-1986
		IE 56046 B1	27-03-1991

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/IB 02/05315

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4559334 A		IT 1173673 B	24-06-1987
		JP 1926846 C	25-04-1995
		JP 6057713 B	03-08-1994
		JP 62294687 A	22-12-1987
		KR 9103118 B1	18-05-1991
		MY 87487 A	31-12-1987
		NO 833531 A ,B,	02-04-1984
		PH 20022 A	01-09-1986
		PT 77426 A ,B	01-10-1983
		SG 61387 G	04-03-1988
		SU 1309911 A3	07-05-1987
WO 02098884 A	12-12-2002	WO 02098884 A1	12-12-2002